CLINICAL TRIAL PROTOCOL

INVESTIGATIONAL PRODUCT:	Licart™ (diclofenac epolamine) topical system
PROTOCOL:	18US-FHp04
PHASE:	III
REGISTRY NAME AND ID (IF APPLICABLE):	clinicaltrials.gov NCT#05171673
TITLE:	A multi-center, prospective, open-label, controlled study of the pharmacokinetics and safety of the Licart™ topical system in pediatric and adult participants with minor soft tissue injuries
SPONSOR:	IBSA Institut Biochimique S.A. [redacted]
SPONSOR STUDY MANAGER:	[redacted]
DOCUMENT VERSION:	1.1
DOCUMENT DATE:	17 February 2022
This study will be performed in compliance with Good Clinical Practices, including the archiving of essential documents	
This protocol is confidential property of IBSA, not to be copied or disclosed to third parties without written authorization from IBSA Institut Biochimique SA.	

DOCUMENT HISTORY

Version Number	Issue Date	Protocol Amendment Number and Description of Change(s)
1.0	26Apr2021	NA
1.1	17Feb2022	Minor amendment n.1: administrative changes ([redacted], information addition of sample blood volume to be drawn during the study, typos corrections.

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with the International Conference on Harmonization Good Clinical Practice (ICH GCP) and the United States (US) Code of Federal Regulations (CFR) 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, 21 CFR Part 11, and/or 21 CFR Part 812.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form(s) will be obtained before any participant is enrolled. Any major amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who already provided consent using a previously approved consent form.

LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ALCOA	Attributable Legible Contemporaneous Original Accurate
ANOVA	Analysis of Variance
aPTT	Activated Partial Thromboplastin Time
AUC	Area Under the Curve
BMI	Body Mass Index
CMH	Cochran Mantel Haenszel
CFR	Code of Federal Regulations
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
eCRF	Electronic Case Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
DHEP	Diclofenac Epolamine
DSMB	Data Safety Monitoring Board
DSU	Drug Safety Unit
EOS	End of Study
EU	European Union
FDA	Food and Drug Administration
FPFV	First Participant First Visit
GCP	Good Clinical Practice
HR	Heart Rate
ICH	International Conference on Harmonization
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
LPLV	Last Participant Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
NSAIDS	Nonsteroidal Anti-Inflammatory Drugs
OTC	Over the Counter
PI	Principal Investigator
PK	Pharmacokinetics
PT	Preferred Term
PTAE	Pre-treatment Adverse Event
RICE	Rest Ice Compression Elevation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction

SBP	Systolic Blood Pressure
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
USPI	United States Prescribing Information
WHO-DRL	World Health Organization – Drug Reference List

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1 PROTOCOL SYNOPSIS

Title:	A multi-center, prospective, open-label, controlled study of the pharmacokinetics and safety of the Licart™ topical system in pediatric and adult participants with minor soft tissue injuries
Protocol:	18US-FHp04
Phase:	III
Study Site(s):	Up to 15 sites in the United States
Study Objectives:	Primary Objective(s): To evaluate the pharmacokinetics and safety of the Licart topical system in pediatric and adult participants with minor soft tissue injuries over a 14-day treatment course. Secondary Objective(s): To evaluate the analgesic effect of the topical system in pediatric and adult participants with minor soft tissue injuries over a 14-day treatment course. To collect principal investigator-reported global response to therapy.
Study Population:	150 male and female participants aged 6-16 and 18-45 with soft tissue injuries meeting the following criteria will be enrolled. **Inclusion Criteria:** 1. Willing to provide written informed consent; 2. Male or female, 6-11 years old; 12-16 years old; or 18-45 years old; 3. BMI <32kg/m^2; 4. Minor soft tissue injury within 96 hours of enrollment; 5. Spontaneous pain of at least moderate intensity (i.e., pain of at least 6 on the Wong-Baker FACES® scale) according to the participant); 6. Clinically significant injury according to the principal investigator; 7. Willing and able to accommodate study requirements for data collection, including return for study Visits 2 and 5; 8. Have access to high-speed internet, a computer, iPad, or android device for telehealth visits; 9. Negative urine pregnancy test at inclusion for females of reproductive potential (started the menstrual cycle);

10. For pediatric and adult females of reproductive potential (started the menstrual cycle): abstinence from sexual intercourse, or use of highly effective contraception for at least 30 days prior to screening, and agreement to use such a method during study participation and for three (3) days following the final topical system application;
11. For pediatric and adult males of reproductive potential: abstinence from sexual intercourse, or use of condoms or other methods to ensure effective contraception with partner during study participation and for three (3) days following the final topical system application; and
12. Able to read and speak English.

Exclusion Criteria:

1. Major soft tissue injury (fractures are only exclusionary if the injury is stabilized with a device, e.g., a hard cast, that cannot be removed to allow a topical system to be applied to the injured area);
2. Open skin lesion or any dermatological condition (e.g., skin infection, eczema) within the injured area;
3. Injury involves the spine, digits, hands, or bottom of foot;
4. Prior injury to the same site within the past 90 days;
5. Three or more other prior injuries (minor or major) to the region in the past;
6. Injury occurred more than 96 hours prior to study entry;
7. Prior use of topical medication to involved area within 48 hours of study entry;
8. Hypersensitivity disorders, including asthma or urticaria, but only if associated with exposure to aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) including diclofenac;
9. Coagulation defects;

	10. Prior use of over the counter (OTC) analgesics or short-acting NSAIDs (ibuprofen, ketoprofen) within 6 hours of study entry (acetaminophen permitted up until the time of study entry); 11. Prior use of narcotic analgesics within seven (7) days of study entry; 12. Prior use of systemic anti-inflammatory steroidal drugs within 60 days of study entry; 13. Prior use of long-acting NSAIDs such as piroxicam or naproxen since injury; 14. Concomitant use of drugs which may be susceptible to interactions with diclofenac, or affect safety if used concomitantly (e.g., serotonin-selective reuptake inhibitors, lithium, digoxin, anticoagulants, antidiabetic agents, cyclosporin, methotrexate, quinolone antimicrobials, other NSAIDs, steroids and diuretics); 15. Participants with mental, behavioral, or neurodevelopmental disorders for which the relevant disorder(s) prevent compliance with the protocol; 16. Documented alcohol or drug abuse within 365 days of study entry; 17. Documented nicotine dependence within 365 days of study entry; 18. Current or prior history of severe cardiac, renal, or hepatic impairment or disease; 19. Severe systemic diseases (e.g., cancer, severe acute infection); 20. Any underlying disease or medication that severely compromises the participant's immune system; 21. Current or prior history of any chronic pain disorder; 22. Current or prior history of gastrointestinal bleeds or, ulcers; 23. Females who are pregnant or breast feeding; or 24. Participation in another clinical trial within 90 days of enrollment.
Study Design:	Open-label, controlled study in pediatric and adult participants with minor soft tissue injuries. One-hundred fifty (150) participants between 6 and 11years old; 12 and 16 years old; and 18 and 45 years old will be

	enrolled, with equal numbers in each of the three age groups. The 50 adults enrolled will serve as the control. Participants will be seen by the principal investigator (PI) or designee at the clinical site, at entry and Visits 2 and 5 following the first topical system application, with the last visit scheduled on either Day 14 or the day after the participant experiences pain resolution. Visits 3 and 4 will be conducted via telehealth. At each study visit, adverse events (AEs) and concomitant medications will be recorded, local tolerability at the application site scored on a 7-point scale, and pain assessed by participants using the Wong-Baker FACES scale. Vital signs will be measured at the screening visit and Visits 2 and 5. Participants will also assess pain twice daily (morning and evening) at home in the Participant Diary using the same Wong-Baker FACES scale. Blood samples will be obtained from each participant at Visit 2, 24 hours (± 1 hour) after initial topical system application at Visit 1, and at the time of study discontinuation (with a topical system in place) for determination of plasma diclofenac concentration and plasma activated partial thromboplastin time (aPTT). At the End-of-Study (EOS) Visit the principal investigator will provide an assessment of global response to therapy on a 5-point scale.
Treatment:	Participants will be asked to apply the Licart topical system once per day for a maximum of 14 days or until pain resolution, whichever occurs first.
Study Assessments:	**Efficacy Assessments** • Plasma diclofenac concentration, 24 hours (± 1 hour) after initial application (Visit 2) and EOS Visit; • Pain score assessment by participant using the Wong-Baker FACES scale: every day (Participant Diary) and study visits on Visits 2, 3, 4 and 5; and • Principal investigator assessment of global response to therapy on a 5-point scale. **Safety Assessments** • Vital signs will be measured at the screening visit and Visit 2 and 5; • AE reporting at each study visit; • Local tolerability on a 7-point scale at Visits

	2, 3, 4 and 5, or the day after pain resolution, with a topical system applied to the injured area; • Plasma diclofenac concentration, 24 hours (±1 hour) after initial topical system application (Visit 2) and EOS Visit; and • Plasma activated partial thromboplastin time (aPTT), 24 hours (±1 hour) after initial topical system application (Visit 2) and EOS Visit.
Primary Endpoint(s):	• Diclofenac pharmacokinetic profile (Pediatric population vs Adult population; Two-sided 90% confidence interval (CI) <4 ng/mL); • Local tolerability; • AEs; and • Activated partial thromboplastin time (aPTT).
Secondary Endpoint(s):	• Participant-reported pain scores; • Global response to therapy; and • Vital signs.
Statistical Analysis:	• All participants who receive at least one topical system will be subjected to classic safety and efficacy analyses. All participants who receive at least one topical system and have at least one blood draw to support determination of plasma diclofenac concentration will be subjected to the pharmacokinetic analysis. An evaluable participant population with adequate compliance and follow-up may also be analyzed; • Continuous variables will be presented as sample size, means, medians, standard deviations, range and 90% CI. Categorical variables will be presented as sample size, number of observations, percentages and exact 90% CI; • The participant population will be stratified by appropriate age categories and the effects of age may be analyzed using Analysis of Variance (ANOVA) or multiple regression methods; • Plasma diclofenac concentration in pediatric participants will be compared with those of adults using repeated measures mixed models (participants will have reached steady-state blood concentration by the time of the first blood draw).

Expected starting date: 2021.	First Participant First Visit (FPFV) expected in April
Expected ending date: December 2023.	Last Participant Last Visit (LPLV) expected in

1.1 OVERALL STUDY SCHEDULE

Visit	**V1**	**V2**	**V3[1]**	**V4[1]**	**V5**
Day of Treatment	**Day 1**	**Day 2**	**Day 4**	**Day 7**	**Day 14[2]**
Informed consent	X				
Demographics	X				
Medical history	X				
Physical exam	X				
Vital signs	X	X			X
Concomitant medication review	X	X	X	X	X
Pregnancy test	X				
Injury characterization	X				
Participant pain assessment[3]	X	X	X	X	X
Verify eligibility criteria	X				
Investigational product dispensed	X	X			
Investigational product administration	X	X	X	X	
Participant Diary activation	X				
Review Participant Diary		X	X	X	X
Adverse event collection	X	X	X	X	X
Investigational product accountability		X	X	X	X
Treatment compliance		X	X	X	X
Local tolerability		X	X	X	X
Blood collection for diclofenac concentration and aPTT		X			X
Principal Investigator assessment of global response to therapy					X
Unused investigational product returned					X

[1] Visits 3 and 4 will be conducted by telehealth.
[2] Day 14 or the day after the participant experienced pain resolution, whichever occurs first.
[3] Pain additionally assessed by the participant twice daily in the Participant Diary.

1.2 ORGANIZATIONAL AND ADMINISTRATIVE STRUCTURE



2 INTRODUCTION

2.1 RATIONALE

[redacted]Minor soft tissue injuries, both in adults and in children/adolescents, result mainly from sports activities, either competitive or recreational, and less frequently during normal daily activities. With over 30 million children participating in sports each year across the United States, many significant sport-related injuries are to be expected, among which mild injuries such as strains, sprains, and contusions predominate (Demorest, 2003).

In recent years, more and more athletes are undertaking intense training at younger ages or participating in multiple sports in one season, thereby exposing themselves to more opportunities for acute injury and increasing their risk for overuse injuries. One study estimated that there is an average of 2.6 million emergency department visits for sports-related injuries per year for individuals aged 5–24 years (Burt ,2001). Across all ages, the peak incidence of emergency department visits for sport-related injuries occurs at ages 5–14 years and declines gradually with age. Visit rates for sports injury are highest for school-age children (5–12 years), adolescents (13–18 years) and young adults (18–24 years) when compared with other age groups (Burt 2001).

It is estimated that 38% of high school children and 34% of middle school children will sustain a physical activity-related injury that will be treated by a doctor or nurse (Hawkins, 2001). It is likely that the actual number of injuries is larger because many either do not seek medical attention or the injuries go unreported (Adirim, 2003). The yearly costs have been estimated to be as high as 1.8 billion US dollars (Aaron, 1997).

There are physical and physiological differences between children and adults that may cause children to be more vulnerable to injury. Factors that contribute to this difference in vulnerability include children have a larger surface area to mass ratio, children have proportionately larger heads, children may be too small for protective equipment, growing cartilage may be more vulnerable to stresses, and children may not have the complex motor skills needed for certain sports until after puberty (Adirim, 2003;Harris, 2000).

Pre-pubescent children are theoretically less likely to sustain injuries due to acute blunt trauma. This is because they generate lower speeds and have less mass and strength. While children generate less force, their bones are softer and more porous, and the tendons have greater strength. This leads to a greater likelihood of fracture, especially at the growth plates. The adolescent athlete, however, is more vulnerable to injury than the prepubescent child because of greater mass and speed and therefore power. Peak muscle strength occurs at peak height velocity for girls and 6–12 months later in boys. This, combined with impulsiveness and recklessness typically seen in teenagers, may increase the likelihood of injury (Adirim, 2003).

The most commonly injured areas of the body include the ankle and knee followed by the hand,

wrist, elbow, shin and calf, head, neck, and clavicle (Rice, 1989). Contusions, sprains, and strains are the most common injuries sustained by young athletes (Adirim, 2003). Contusions are bleeds into the muscle and soft tissues and are often referred to as bruises. A sprain is any injury to a ligament that can range from a mild stretch to a complete disruption of the ligament. A strain is an injury caused by stretching or exerting a muscle beyond its limits. Contusions are most common in contact sports such as football and hockey where collision with other players is expected. Muscle strains can occur in any athlete, but especially in runners and in children participating in sports where running is part of the game, such as soccer and basketball. Muscle strains are more common in older adolescents and adults, whereas strains at an apophysis or apophysitis are more common in early adolescents. Recommended treatment includes rest, ice, compression, and elevation (RICE) of the affected body part. Athletes can return to play when pain has subsided, and strength and range of motion in the affected extremity is restored. Acute ankle injuries are common in young athletes. The most common ankle sprains occur when the foot is plantar flexed and inverted. This leads to a lateral ankle sprain. Early treatment of ankle sprains includes RICE plus protection. After the first few days, the athlete should begin range of motion and flexibility exercises and strengthening as tolerated. The athlete can gradually return to play if range of motion, strength and sports-specific skills are restored (Adirim, 2003).

It is difficult to obtain data on the relative risks (based on injury rates) of various types of sports for youth because exposure data across sports are limited. The most frequent sports-related activities causing emergency department visits include pedal cycling, basketball, and football (Burt 2001; Cheng, 2000). However, this does not mean that these activities are more dangerous than others as there may be more people engaging in these activities. Surveillance of high school organized sports has found that football had the highest injury rate with 41–61% of athletes injured annually (Garrick, 1978; McLain, 1989). Other sports with high annual injury rates include

wrestling and gymnastics (40–46%), basketball (31–37%), volleyball, baseball, soccer, cross country, softball, and track (7–18%) (Aaron, 1997).

2.2 BACKGROUND INFORMATION

[redacted]

2.3 RISK-BENEFIT ASSESSMENT

2.3.1 Known Potential Risks

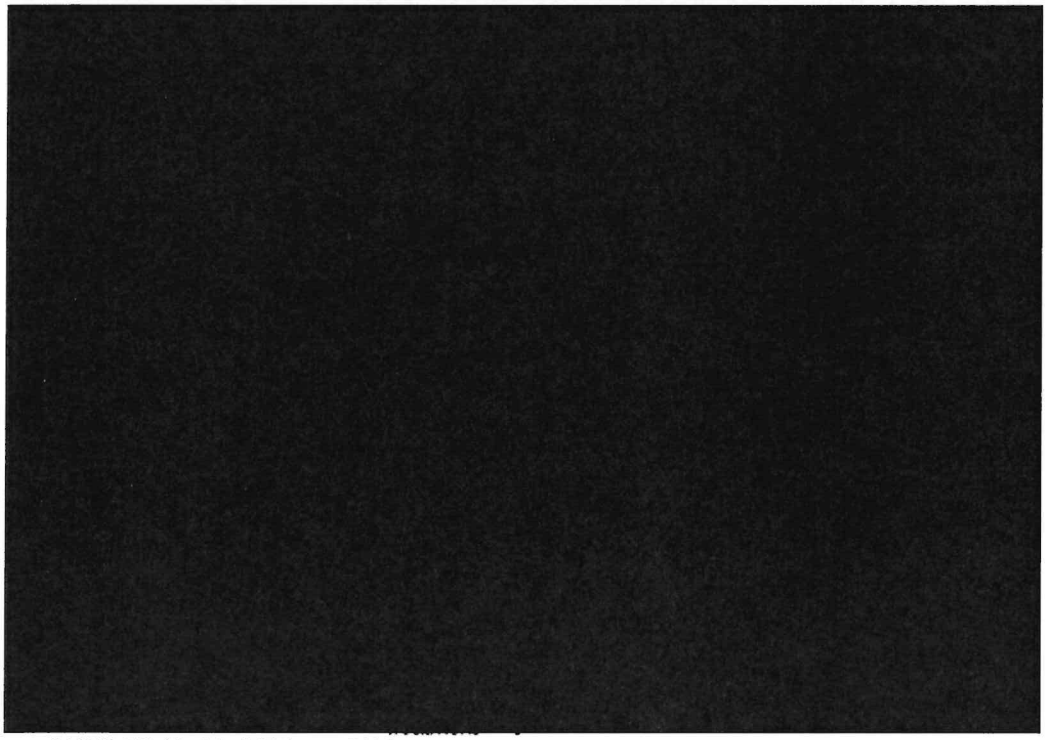
[redacted]

[redacted]

2.3.2 Known Potential Benefits

[redacted]

[redacted]



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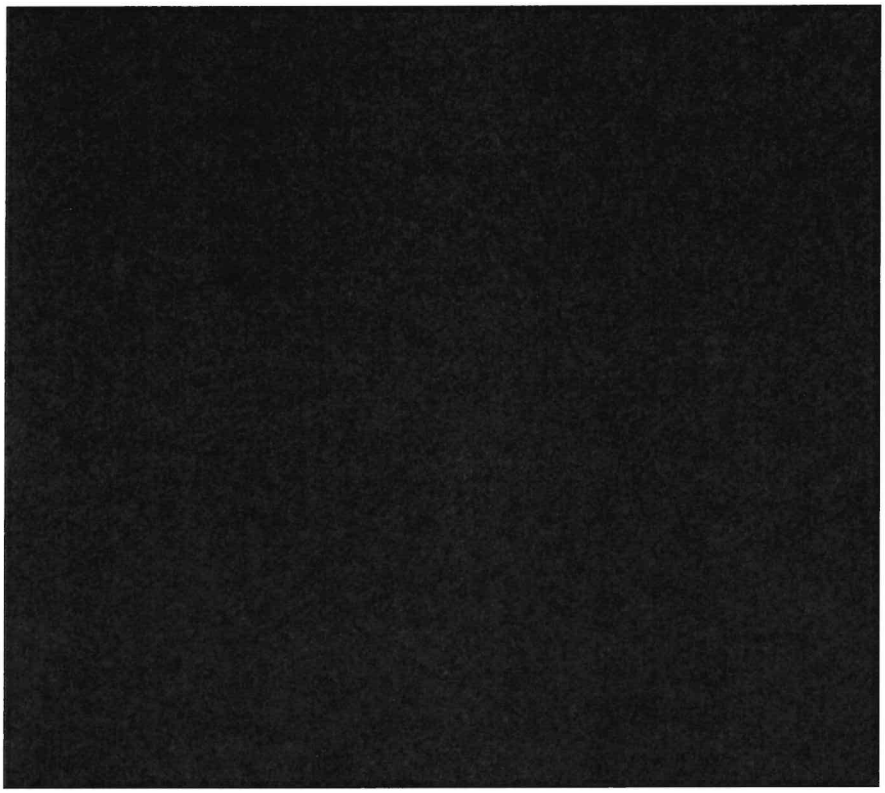


2.3.3 Assessment of Potential Risks and Benefits

The purpose of this study is to evaluate the pharmacokinetics and safety of the Licart topical system for the treatment of minor soft tissue injuries (such as sprains, strains, and contusions) in pediatric participants 6-16 years old and adult participants 18-45 years old. [redacted]

3 TRIAL OBJECTIVES

3.1 PRIMARY OBJECTIVE(S)

To evaluate the pharmacokinetics and safety of the Licart topical system in pediatric and adult participants with minor soft tissue injuries over a 14-day treatment course.

3.2 SECONDARY OBJECTIVE(S)

To evaluate the analgesic effect of the Licart topical system in pediatric and adult participants with minor soft tissue injuries over a 14-day treatment course. To collect principal investigator-reported global response to therapy.

4 TRIAL DESIGN

4.1 OVERALL DESIGN

This is an open-label, controlled study in pediatric and adult participants with minor soft tissue injuries. One-hundred fifty (150) participants between 6 and 11 years old; 12 and 16 years old; and 18 and 45 years old will be enrolled, with equal numbers in each of the three age groups. The 50 adults enrolled will serve as the control. Participants will be seen by the PI or designee[4] at the clinical site, at entry and Visits 2 and 5 following the first topical system application, with the last visit scheduled on either Day 14 or the day after the participant experiences pain resolution. Visits 3 and 4 will be conducted via telehealth. At each study visit, adverse events (AEs) and concomitant medications will be recorded, local tolerability at the application site scored on a 7-point scale, and pain assessed by participants using the Wong-Baker FACES scale. Vital signs will be measured at the screening visit and Visits 2 and 5. Participants will also assess pain twice daily (morning and evening) at home in the Participant Diary using the same Wong-Baker FACES scale. Blood samples will be obtained from each participant at Visit 2, 24 hours (± 1 hour) after the initial topical system application at Visit 1, and at the time of study discontinuation (with a topical system in place) for determination of plasma diclofenac concentration and plasma activated partial thromboplastin time (aPTT). At the End-of-Study (EOS) Visit, the principal investigator will provide an assessment of global response to therapy on a 5-point scale.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Participant Age: For children, the participants will be 6 to 16 years old, the lower limit representing the approximate age at which children have sufficient size and aggressiveness to be at increased risk of minor soft tissue injuries requiring medical intervention. For adults, the age will be 18 to 45, with the upper limit intended to reduce the potential variability in skin histology based on age.

[4] Designee means clinical site staff delegated by the PI to perform one or more study related activities. The delegated activities of the designees should be documented in the site delegation form.

Eligibility Requirement: Although females of child-bearing potential in the 12 to 16 year old age group will be given a urine pregnancy test, they will not be required to use a specific method of contraception (other than recommending abstinence) for the following reasons: (1) the likelihood of a female in this age group becoming pregnant during a 14-day protocol is remote; (2) even if they become pregnant, systemic exposure to Licart subsequent to topical dosing with Licart topical system will be minimal; and (3) a contraception requirement (e.g., oral contraceptive, intrauterine device, etc.) is likely to exclude virtually all females in this age group. [redacted]

Choice of Control Group: An equal number of adult participants allows for a more direct, contemporaneous, and accurate comparison of the study endpoints, in particular, the pharmacokinetic profile.

aPTT Measurement: aPTT will be measured to assess the potential for heparin to be absorbed into systemic circulation and alter endogenous clotting pathways.

4.3 JUSTIFICATION OF DOSE

[redacted]

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if they have completed all phases of the study including the EOS Visit or the last scheduled procedure shown in the Schedule of Activities (See **Section 1.1**). The end of study is defined as the completion of the last participant's EOS Visit or last scheduled procedure.

5 SELECTION OF POPULATION

5.1 INCLUSION CRITERIA

Participants must satisfy the following criteria to be enrolled in the trial:

1. Willing to provide written informed consent;
2. Male or female, 6-11 years old; 12-16 years old; or 18-45 years old;
3. BMI <32kg/m^2;
4. Minor soft tissue injury within 96 hours of enrollment;

5. Spontaneous pain of at least moderate intensity (i.e., pain of at least 6 on the Wong-Baker FACES® scale) according to the participant);
6. Clinically significant injury according to the principal investigator;
7. Willing and able to accommodate study requirements for data collection, including return for study Visits 2 and 5;
8. Have access to high-speed internet, a computer, iPad, or android device for telehealth visits;
9. Negative urine pregnancy test at inclusion for females of reproductive potential (started the menstrual cycle);
10. For pediatric and adult females of reproductive potential (started the menstrual cycle): abstinence from sexual intercourse or, use of highly effective contraception for at least 30 days prior to screening, and agreement to use such a method during study participation and for three (3) days following the final topical system application.
11. For pediatric and adult males of reproductive potential: abstinence from sexual intercourse, or use of condoms or other methods to ensure effective contraception with partner during study participation and for three (3) days following the final topical system application; and
12. Able to read and speak English.

5.2 EXCLUSION CRITERIA

Participants who meet any of the following criteria must be excluded:

13. Major soft tissue injury (fractures are only exclusionary if the injury is stabilized with a device, e.g., a hard cast, that cannot be removed to allow a topical system to be applied to the injured area);
14. Open skin lesion or any dermatological condition (e.g., skin infection, eczema) within the injured area;
15. Injury involves the spine, digits, hands, or bottom of foot;
16. Prior injury to the same site within the past 90 days;
17. Three or more other prior injuries (minor or major) to the region in the past;
18. Injury occurred more than 96 hours prior to study entry;
19. Prior use of topical medication to involved area within 48 hours of study entry;
20. Hypersensitivity disorders, including asthma or urticaria, but only if associated with exposure to aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) including diclofenac;
21. Coagulation defects;
22. Prior use of over the counter (OTC) analgesics or short-acting NSAIDs (ibuprofen, ketoprofen) within six (6) hours of study entry (acetaminophen permitted up until the time of study entry);
23. Prior use of narcotic analgesics within seven (7) days of study entry;
24. Prior use of systemic anti-inflammatory steroidal drugs within 60 days of study entry;
25. Prior use of long-acting NSAIDs such as piroxicam or naproxen since injury;

26. Concomitant use of drugs which may be susceptible to interactions with diclofenac, or affect safety if used concomitantly (e.g., serotonin-selective reuptake inhibitors, lithium, digoxin, anticoagulants, antidiabetic agents, cyclosporin, methotrexate, quinolone antimicrobials, other NSAIDs, steroids and diuretics);
27. Participants with mental, behavioral, or neurodevelopmental disorders for which the relevant disorder(s) prevent compliance with the protocol;
28. Documented alcohol or drug abuse within 365 days of study entry;
29. Documented nicotine dependence within 365 days of study entry;
30. Current or prior history of severe cardiac, renal, or hepatic impairment or disease;
31. Severe systemic diseases (e.g., cancer, severe acute infection);
32. Any underlying disease or medication that severely compromises the participant's immune system;
33. Current or prior history of any chronic pain disorder;
34. Current or prior history of gastrointestinal bleeds or ulcers;
35. Females who are pregnant or breast feeding; or
36. Participation in another clinical trial within 90 days of enrollment.

5.3 LIFESTYLE CONSIDERATIONS

Potential participants that are known to abuse alcohol or drugs, or are dependent upon nicotine, will be excluded from participating in this trial.

5.4 SCREEN FAILURES

Screen failures are participants who consent to participate in the study but are not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting and respond to potential queries from regulatory authorities; this information includes demographics, screen failure details, eligibility criteria, and serious adverse events (SAEs).

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

This study will enroll 150 participants with minor soft tissue injuries, with 50 participants in each of the following three age groups: 6 and 11 years old, 12 and 16 years old, and 18 and 45 years old. There will be no formal plan to ensure equivalent enrollment based on gender or ethnicity.

The accident-based nature of soft tissue injuries necessary for study eligibility eliminates several of the common tactics typically used to support recruitment of potential participants. Consequently, the primary focus will be to identify and recruit up to 15 sites that have a high volume of potential participants presenting with soft tissue injuries. In addition, the following recruitment tactics may be used:

- In-clinic flyer(s) describing the study;
- Email or calls to the clinic patient database describing the study;
- Radio and/or television advertisements; or
- Social media platforms.

Given that children below the age of consent will be enrolled in this study, appropriate consent documents from the overseeing Institutional Review Board (IRB) will be utilized to ensure that the child and/or parent/legally authorized representative are aware of the potential risks and benefits of the study procedures.

Study participants and their parent(s)/legally authorized representative(s) will be provided monetary compensation for time and travel during study participation; the relative amounts will be agreed upon with the overseeing IRB. Compensation will be remitted directly to the parent/legal authorized representative at the conclusion of study participation.

6 TREATMENTS

6.1 INVESTIGATIONAL PRODUCT (IP)

6.1.1 Description of Investigational Product

The Licart topical system was designed to deliver the nonsteroidal anti-inflammatory drug (NSAID) diclofenac to the site of a minor soft tissue injury through topical application. This investigational product (IP) is a 10 cm x 14 cm topical system comprised of an adhesive material containing 1.3% diclofenac epolamine that is bound to a non-woven polyester felt backing and covered with a polypropylene film release liner. The release liner is removed prior to topical application to the skin.

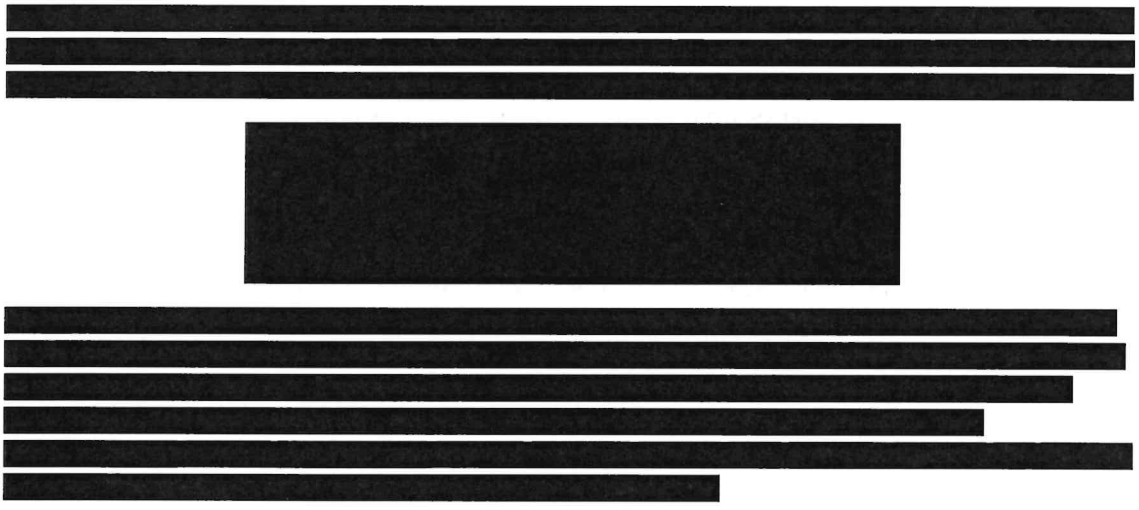
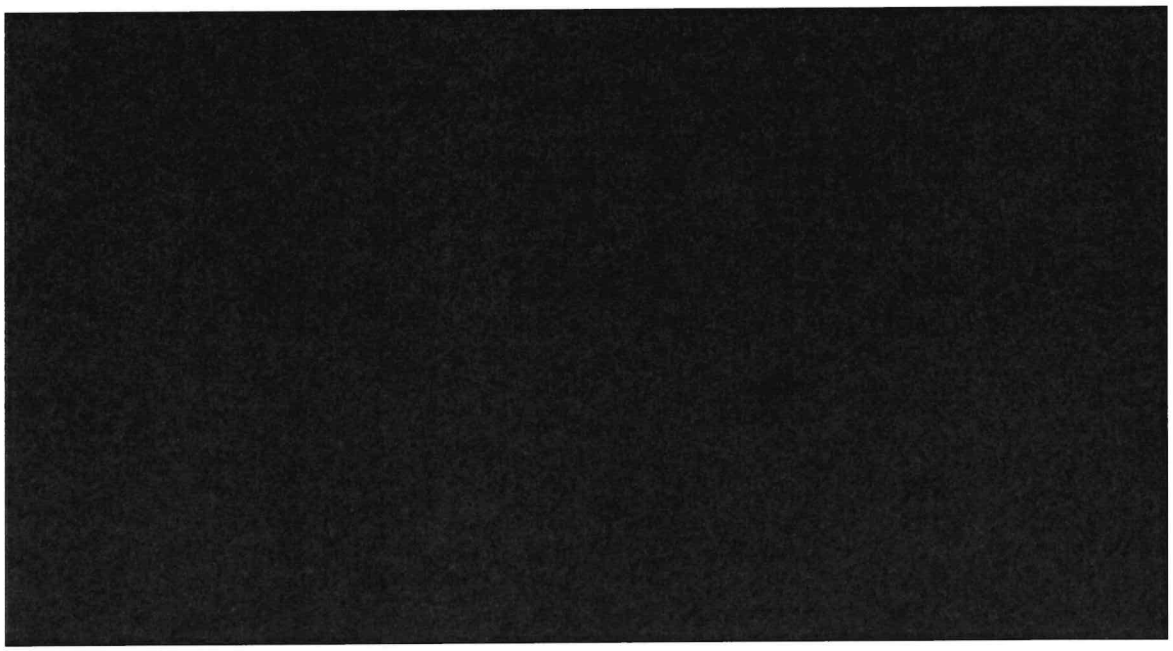


Table 6.1.1.1 Investigational Product Characteristics



6.1.2 Dosage and Administration

The PI or designee will train participants on proper topical system application ( ). A single topical system will be applied directly to the injured area once per day at approximately the same time each day; treatment will proceed for a maximum of 14 days, or until no longer required for pain management. The topical system may be cut to a customized dimension if the opposed ends overlap, and if this customization is performed, the resulting dimensions will be recorded in the electronic case report form (eCRF). As needed, the topical system may be overlayed with an elastic net provided in the participant kit.

The topical system should be affixed to the participant's skin for no longer than 24 hours, and prior to bathing, showering, swimming, etc., it should be removed, and a fresh topical system applied to the injured area after the skin is thoroughly dried. Commencing with the third day of treatment, participants should replace the topical system at the same time each morning for the duration of the study. If a topical system should become detached because of participant activity, a fresh topical system should be reapplied as soon as possible, but only after the application surface has been cleaned and dried. The maximum number of topical systems that can be applied per day is two.

6.2 PREPARATION, HANDLING, STORAGE AND ACCOUNTABILITY

6.2.1 Packaging and Labelling



6.2.2 Preparation Onsite Not applicable.

6.2.3 Receipt, Storage and Accountability

[redacted]

6.2.4 Treatment Compliance

At each study visit, the PI or designee will document if a topical system is applied to the injured area and whether the system needed to be cut. The sponsor will formally assess treatment compliance at the end of the study through review of IP accountability records for each participant.

6.2.5 Precautions and Overdosage

When systemic signs of intolerance are reported (e.g., severe local irritation or generalized allergic reaction), treatment will be suspended immediately, and the participant should return to the clinical site before being discontinued from the study. The participant will be followed until complete resolution of the event. Additional information concerning relevant precautions and the procedures to be undertaken in the event of overdosage can be found in the Investigator Brochure.

6.3 CONCOMITANT MEDICATIONS AND STUDY RESTRICTIONS

6.3.1 Concomitant Medications

Participants will be allowed to use any concomitant medication necessary for the treatment of pre-existing concomitant pathologies or for intercurrent diseases that are not exclusionary. All concomitant medications will be recorded in the eCRF.

Participants will also be allowed to use conventional ancillary treatments, such as RICE or ambulatory aids, such as crutches, are permitted during the study, and their use will be captured in the eCRF.

Participants will not be allowed to use the following:

- Any systemic or topical medication with known analgesic effects other than the IP;
- Any topical product on the injured area;
- Physiotherapy (e.g., ultrasound, electrotherapy, ionization);
- Alternative medical practice (e.g., acupuncture, homeopathy, mesotherapy);
- Drugs which may be susceptible to interaction with diclofenac or affect safety if used concomitantly (see **Section 5.2**); and
- Overlay material other than the provided elastic nets (see **Section 6.1.2** and **6.2.1**).

6.3.2 Rescue Medication

There is no formal rescue medication provided during the study. Participants are free to withdraw at any time if they consider their pain relief insufficient, and, if necessary, the PI may suggest an alternative treatment regimen.

6.4 TREATMENT ALLOCATION AND RANDOMIZATION PROCEDURES Not applicable.

6.5 EMERGENCY CODE AND UNBLINDING PROCEDURES Not applicable.

7 DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION/WITHDRAWAL

Participation will be discontinued for any of the following reasons:

- Protocol completion;
- Voluntary participant/parent/legally authorized representative withdrawal for any reason;
- PI's discretion;
- An AE, including onset or worsening of a concomitant illness, that is considered by the PI to be incompatible with continuation in the study;
- Administration of a drug that is not permitted according to the exclusion criteria;
- Failure to comply with the requirements of the protocol or major protocol deviation (e.g., inclusion error, evidence of noncompliance with exclusion/inclusion criteria during the study, participant misses study visits or/ and/or failure to take assigned medication, or provide blood sample as required, female becomes pregnant, etc.)

- Re-injury of the same anatomical location;
- Lost to follow-up; or
- Participant death.

Participants who provide informed consent, receive the IP, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced to assure that a total of 150 participants will be evaluable at the end of the study. Replacements may be allocated to any of the sites participating in the study.

7.2 PREMATURE TERMINATION

The trial may be suspended temporarily or terminated prematurely if there are any relevant medical or ethical concerns, or if completing the trial is no longer practicable. If such action is taken, the reasons for terminating the trial must be documented in detail and submitted to the overseeing IRB and FDA. All trial participants still under treatment at the time of termination will undergo a final examination, the results of which will be documented in the eCRF.

7.3 LOST TO FOLLOW-UP

The PI or designee must take the following actions if a participant fails to return to the site for a required study visit:

- Attempt to contact the participant and reschedule the missed visit as soon as possible; counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study;
- Make every effort to regain contact with the participant. Where possible, three (3) telephone calls should be made and, if necessary, a certified letter sent to the participant's last known mailing address. These contact attempts should be documented in the source documents and eCRF.

Should the participant continue to be unreachable, they will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

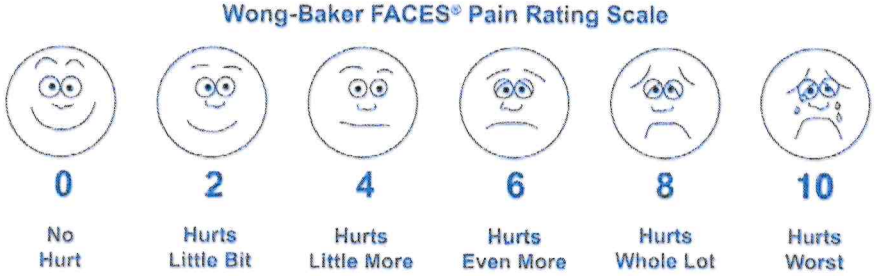
8.1 EFFICACY ASSESSMENTS

- Plasma diclofenac concentration: Two blood samples, up to a total of 13 mL, will be collected from each participant, the first at Visit 2, 24 hours (± 1 hour) after initial topical system application on Visit 1, and the second the day following pain resolution or Day 14, whichever comes first, both while the topical system is still applied to the injured area. Specific instructions for sample collection, processing and shipping will be provided in the study manual. Plasma diclofenac concentration will be determined using a validated analytical method.

A two timepoint pharmacokinetic profile will be generated for pediatric and adult participants over the 14-day treatment course. The demonstrated efficacy of the Licart topical system in adults will be extrapolated to children based on the similarity of the aforementioned pharmacokinetic profiles (Pediatric population *vs.* Adult population; two-sided 90% CI <4 ng/mL; see **Section 9.4.3.2**). This approach to establishing efficacy is acceptable because systemic diclofenac concentration serves as a surrogate for, and correlate of, tissue diclofenac concentration, a more likely predictor of efficacy.

- Pain: Pain will be assessed by study participants on study Visits 2, 3, 4 and 5 and daily in the Participant Diary according to the Wong-Baker FACES scale in **Figure 8.1.1**.

Figure 8.1.1: Wong-Baker FACES Pain Rating Scale



- Global response to therapy: Global response to therapy will be assessed at the EOS Visit by the PI or designee according to the 5-point scale in **Table 8.1.2**.

Table 8.1.2: Global Response to Therapy

Description	Score
No clinical improvement in pain intensity and/or functional performance	1 ❑
Slight clinical improvement in pain intensity and/or functional performance	2 ❑
Moderate clinical improvement in pain intensity and/or functional performance	3 ❑
Marked clinical improvement in pain intensity and/or functional performance	4 ❑
Restoration of normal functional performance in the absence of any pain	5 ❑

8.2 SAFETY ASSESSMENTS

- Vital signs: Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR), will be measured after 5 minutes at rest in the sitting position by delegated site personnel at Visit 1 and Visits 2 and 5.

- Adverse events: The occurrence, frequency, nature, and severity of all adverse events that occur after written informed consent has been provided will be documented for each

participant. At each study visit the PI or designee will ask the participant about any untoward experiences since the previous visit.

- Local tolerability: The application site will be assessed by the PI or designee according to the scoring schema in **Table 8.2.1**. This evaluation will be performed on Visits 2, 3, 4 and 5 (and/or the day after pain resolution).

Table 8.2.1: Application Site Scoring Schema

Response	Visible Change	Grade
Absent	None	0
Vascular Dilation Stage	Faint redness (not considered clinically relevant)	1
	Moderate redness	2
	Intense redness	3
Infiltration Stage	Redness with edema or papules	4
	Redness with weeping vesicles, blisters, or bullae	5
	Redness with extension of effect beyond margin of contact site	6

- Plasma diclofenac concentration: Two blood samples, up to a total of 13 mL, will be collected from each participant, the first at Visit 2, 24 hours (± 1 hour) after initial topical system application on Visit 1, and the second the day following pain resolution or Day 14, whichever comes first, both while the topical system is still applied to the injured area. A plasma sample will be generated and used to assess the amount of diclofenac using a validated analytical method. Specific instructions for sample collection, processing and shipping will be provided in the study manual.

- Activated partial thromboplastin time (aPTT): Two blood samples, up to a total of 13 mL, will be collected from each participant, the first at Visit 2, 24 hours (± 1 hour) after initial topical system application on Visit 1, and the second the day following pain resolution or Day 14, whichever comes first, both while the topical system is still applied to the injured area. A plasma sample will be generated and used to assess aPTT according to a validated analytical method. Specific instructions for sample collection, processing and shipping will be provided in the study manual.

8.2.1 Overall Study Schedule

The study schedule is summarized in **Section 1.1** and briefly described below.

8.2.2 Screening/Inclusion – Visit 1 (Day 1)

After a potential participant and parent/legally authorized representative has been informed both verbally and in writing about the study objectives and procedures and written informed consent to participate in the study has been obtained, the participant will be assigned a screening number and compliance with inclusion/exclusion criteria will be assessed. The PI or designee will do the

following to assess eligibility:

- Assign a progressive participant number to each participant to serve as a study identifier;
- Record demographic data, medical history, and lifestyle (including any alcohol, drug, or nicotine usage);
- Perform a physical exam, including measurement of vital signs (blood pressure, heart rate), height, weight, and a general assessment of all body systems;
- Record prior and concomitant treatments, including those used to treat the injury prior to study entry;
- Perform a urine pregnancy test for all females of childbearing potential;
- Diagnose the injury as a strain, sprain, contusion or "other";
- Characterize the injury;
- Examine the injured area for the presence of open skin lesions or pre-existing dermatological conditions; and
- Record participant-reported baseline pain on the Wong-Baker FACES scale.

If the participant is found to be eligible for the trial, the PI or designee will do the following:

- Supply the participant with an investigational product (IP) kit containing five (5) sealed envelopes with five (5) topical systems each for a total of 25 topical systems, and five (5) elastic nets and breathable paper tape to maintain the topical system in place if needed. One (1) envelope with five (5) topical systems will be retained by the clinical site for use during Visit 1 and Visit 2, and will be supplied to the participant at the end of Visit 2;
- Apply the first topical system to demonstrate proper technique for subsequent application by the participant and/or the parent/legally authorized representative;
- Instruct the participant to maintain the topical system in place until the blood sample is collected during Visit 2;
- Provide access to the electronic Participant Diary to record daily treatment compliance and injury-related pain; and
- Schedule the next visit 24 hours (± 1 hour) after the initial topical system application.

8.2.3 Treatment Phase – Visit 2 (Day 2)

Participants and their parents/legally authorized representatives will return to the clinical site, and the PI or designee will do the following:

- Measure vital signs;
- Discuss new concomitant medications, adverse events, and treatment compliance;
- Review Participant Diary;
- Confirm that a topical system is applied to the injured area
- Collect blood samples and process according to the study manual;

- Remove the topical system and assess local tolerability on a 7-point scale, followed by application of a new topical system by the participant and/or the parent/legally authorized representative;
- Record participant-reported pain using the Wong-Baker FACES scale;
- Investigational product accountability;
- If the participant should continue their participation in the study, dispense the retained envelope and schedule the next visit (Visit 3) on Day 4 (i.e., 4th day of treatment) at approximately the same time of day as Visit 2;
- Inform the participant to replace the topical system at the same time each morning for the duration of the study; and
- If pain management is no longer required, discontinue the participant, and perform all EOS activities.

8.2.4 Treatment Phase – Telehealth Visit 3 (Day 4)

The PI or designee should perform the same activities described for Visit 2, except:

- Vital signs will not be measured;
- Blood should not be collected; and
- Visit 4 should be scheduled for Day 7.

8.2.5 Treatment Phase – Telehealth Visit 4 (Day 7)

The PI or designee should perform the same activities described for Visit 2 except:

- Vital signs will not be measured;
- Blood should not be collected; and
- Visit 5 should be scheduled for Day 14.

8.2.6 End-of-Study (EOS) Visit – Visit 5 (Day 14) or Day after Pain Resolution

Participants and their parents/legally authorized representatives will return to the clinical site for the EOS Visit on Day 14, or the day after pain resolution, whichever comes first. It is important that participants maintain uninterrupted dosing and return with a topical system applied to the injured area to allow for determination of plasma diclofenac concentration and aPTT. If pain resolution occurs before Day 14, or if the participant is discontinued for another reason, the participant and parent/legally authorized representative will be asked to call the PI or designee to schedule the EOS Visit for the following day.

The PI or designee will do the following at the EOS Visit:

- Measure vital signs;

- Discuss new concomitant medications, adverse events and determine treatment compliance;
- Review Participant Diary;
- Confirm that a topical system is applied to the injured area;
- Collect blood sample and process according to study manual;
- Remove the topical system and assess local tolerability on a 7-point scale;
- Record participant-reported pain using the Wong-Baker FACES scale;
- Record investigator-reported global response to therapy on a 5-point scale
- Investigational product accountability; and
- Collect unused IP

8.2.7 Follow-up

No follow-up visits are planned for this study. An exception will be made in case of an SAE or adverse drug reaction (ADR) that is considered not resolved at the EOS Visit on Day 14. Participants will be contacted by the PI or designee by telephone and, when necessary, a follow-up in-clinic visit will be scheduled. During the follow-up visit no information other than the AE/SAE status will be recorded. All SAEs will be followed until resolution or stabilization (See **Section 8.3.7**).

8.2.8 Other Study Material

T[redacted]

- [redacted]

8.3 ADVERSE EVENT DESCRIPTION AND REPORTING

8.3.1 Adverse Events (AEs)

An adverse event is any untoward medical occurrence in a clinical trial subject, whether or not

there is a suspected causal relationship between the event and the investigational product. Adverse events include exacerbation of a pre-existing medical condition, that is, the condition has increased in severity, frequency and/or duration. A pre-existing condition that did not deteriorate during the study, but was treated with a medical or surgical procedure, should not be recorded as an adverse event. However, the procedure itself should be in the CRF.

An adverse drug reaction (ADR) is any adverse event with a suspected causal relationship to the investigational product. This means that there is at least reasonable evidence that the event might have been elicited by administration of the investigational product.

8.3.2 Serious Adverse Events (SAEs)

Serious adverse events are a subset of adverse events that resulted in one of the following outcomes:

- Death;
- Life-threatening illness or injury (i.e., the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe);
- Inpatient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability or incapacity;
- A congenital anomaly or birth defect; or
- An important medical event (i.e., an event that jeopardize the patient or may require intervention to prevent one of the other outcomes listed above).

A serious adverse reaction (SAR) is any serious adverse event with a suspected causal relationship to the investigational product. This means that there is at least reasonable evidence that the event might have been elicited by administration of the investigational product.

8.3.3 Causality Assessment and Classification

The PI must make a causality assessment for each adverse event experienced by a study participant following at least one dose of investigational product according to the following guidance. However, any adverse event that occurs between written informed consent and administration of the first dose of investigational product will be considered a pre-treatment adverse event (PTAE), and this option should be selected in the applicable form rather than making a causality assessment.

- Certain: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. The clinical event, including laboratory test abnormality, occurs in a plausible time relationship to investigational product administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible.

The event must be pharmacologically or phenomenologically[5] definitive, with use of a satisfactory re-challenge procedure if necessary.

- Probable: There is evidence to suggest a causal relationship and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test, occurs within a reasonable time after administration of the investigational product, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfil this definition.
- Possible: There is some evidence to suggest a causal relationship; however, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant treatments). The clinical event, including an abnormal laboratory test, occurs within a reasonable time after administration of investigational product, but could be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- Unlikely: There is another reasonable explanation for the event occurrence. A clinical event, including an abnormal laboratory test, whose temporal relationship to investigational product administration makes a causal relationship improbable, and which other drugs, chemicals or underlying disease provide plausible explanations.
- Not related: There is no evidence of any causal relationship between the clinical event and investigational product administration, and/or sufficient information exists to indicate that the event is related to another etiology.

8.3.4 Severity Classification

Regardless of the classification of an adverse event as serious or non-serious, the severity of an adverse event will be rated according to the following definitions:

- Mild: Symptom barely noticeable to participant and does not interfere with participant's daily activities. Minimal or no treatment typically needed for relief of symptom.
- Moderate: Symptom may cause some discomfort and may interfere with participant's daily activities. The subject can continue the study, even if treatment of symptom may be needed.

[5] A specific medical disorder or a recognized pharmacological phenomenon (e.g., gray baby syndrome and chloramphenicol, or anaphylaxis immediately after the administration of a drug that had been given previously). If this criterion is not met, the relationship between the investigational product and the event onset can never be classified as 'Certain', even with positive

rechallenge.

- Severe: Symptom causes severe discomfort and interrupts the participant's daily activities. They may be of such severity that investigational product administration must be stopped, and the participant may be treated for symptoms and/or hospitalized.

It should be noted that a severe adverse event does not have to be serious in nature and vice versa. Contrary to the other two classifications (seriousness and causality), the classification of severity does not have any impact on reporting procedures.

8.3.5 Reporting

[redacted]

[redacted]

8.3.6 Pregnancy

Within 24 hours of the discovery of a pregnant participant, the PI or designee will complete a Pregnancy Form and submit it to the sponsor according to guidance for serious adverse event reporting in **Section 8.3.5**.

8.3.7 Follow-up

Following reporting of an adverse event, participants will be followed for at least three (3) days, which is equivalent to 5-times the half-life of Licart following application of a topical system. Serious adverse events, serious adverse reactions (SARs) and SUSARs should be followed until resolution or stabilization. Medical or surgical procedures that occur during the study that did not result from an AE or SAE will not require follow-up. Pregnancies will be followed to delivery, if possible.

9 DATA MANAGEMENT AND STATISTICAL ANALYSIS

9.1 DATA COLLECTION

Source data are all information, original records of clinical findings, observations, or other activities necessary for reconstruction of a clinical trial. Source data can be either electronic or handwritten, and includes but is not limited to hospital records, clinical and office charts, progress notes, laboratory notes and records, pharmacy records, informed consent forms, participant diaries and notes, and study visit worksheets.

Designated clinical site personnel will be responsible for data collection under the supervision of the PI, who is ultimately responsible for ensuring the data are attributable, legible, contemporaneous, original, and accurate (ALCOA). To the extent possible, all study data will be

entered directly into the eCRF by the PI or designee and such data will be considered electronic source (eSource). Study data will also be collected in an electronic Participant Diary and such data will be transmitted directly to the eCRF through a native integration between these systems. Although designated clinical site personnel are not directly responsible for collection of diary data, they should nonetheless review the diaries to ensure collection of required data. Plasma diclofenac levels and aPTT values obtained from the central laboratory will be transmitted into the eCRF through an inter-vendor integration.

When it is not possible to enter data directly into the eCRF the PI or designee may use paper worksheets that will be considered source. All paper source documents should be completed in a neat, legible manner to ensure accurate interpretation and transcription into other media, as applicable. Designated clinical site personnel will be responsible for entry of all relevant paper source data into the eCRF under the supervision of the PI. Data entry should be completed contemporaneously with each visit; preferably within 24 hours but, not exceeding three days.

All eCRF users will receive an EDC User Manual and training on system use prior to enrollment of the first participant. Access to the eCRF will be controlled by the sponsor or designee through provision of user-specific login credentials that will only be provided after documentation of eCRF training. All personnel authorized to make entries in the eCRF will be listed by name, title, signature, and initials. The list should be updated during the study, if needed.

The PI and/or designated clinical site personnel should immediately alert the clinical monitor and/or sponsor designee about eCRF operational issues. In the unlikely event that the eCRF is unavailable for an extended period of time, the clinical monitor may direct designated clinical site personnel to utilize paper CRFs for data collection.

All data originators (i.e., PI, designee(s) and participants) at each clinical site will be documented and made available, if needed. Each data element in the eCRF will have an associated identifier comprised of a data originator, date/time stamp, and clinical trial participant, and both the data element and identifier will be present in a human-readable audit trail.

9.2 DATA MANAGEMENT

The computer system(s) used in this study will be designed and validated according to contemporary standards, including 21 CFR Part 11, prior to deployment. The eCRF will be designed with internal edit checks, including but not limited to automatic range checks, to promote data quality. In addition, manual queries can be created in the eCRF by clinical monitors or other sponsor designee(s). All changes in the eCRF will be documented in an audit trail that cannot be manipulated by system users. Following data review and resolution of queries, as applicable, the PI will electronically sign each participant's study record, thereby locking the dataset and preventing additional changes. The electronic signature represents the PI's attestation to the accuracy and completeness of the data and has the same legal meaning as a hand-written signature.

After database cleaning has occurred and a blind data review has been performed, the trial database will be considered locked. Following finalization of the Statistical Analysis Plan (SAP), the statistical analyses will be performed. Any further modification of recorded data that requires the database to be unlocked and subsequently re-locked will be documented.

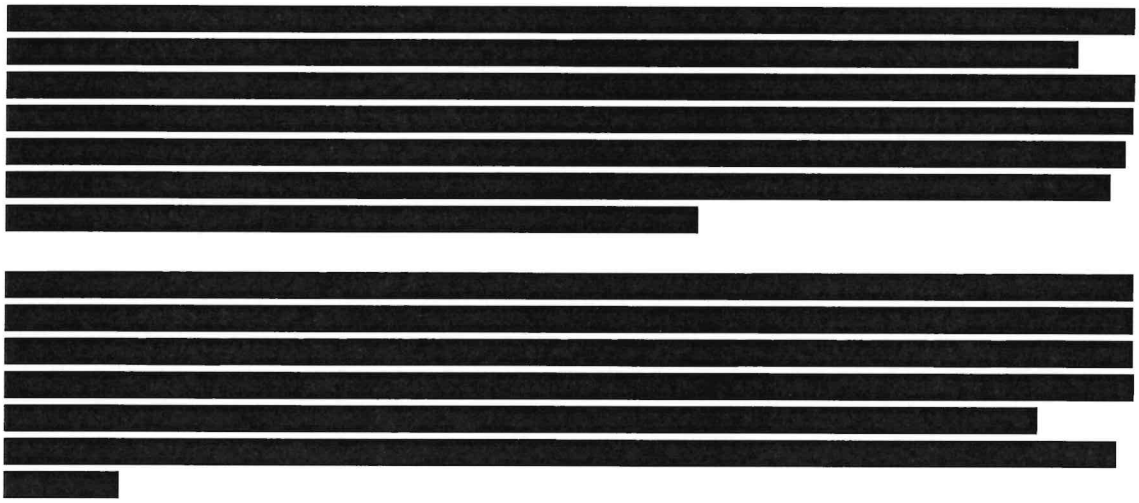
9.3 CODING DICTIONARIES

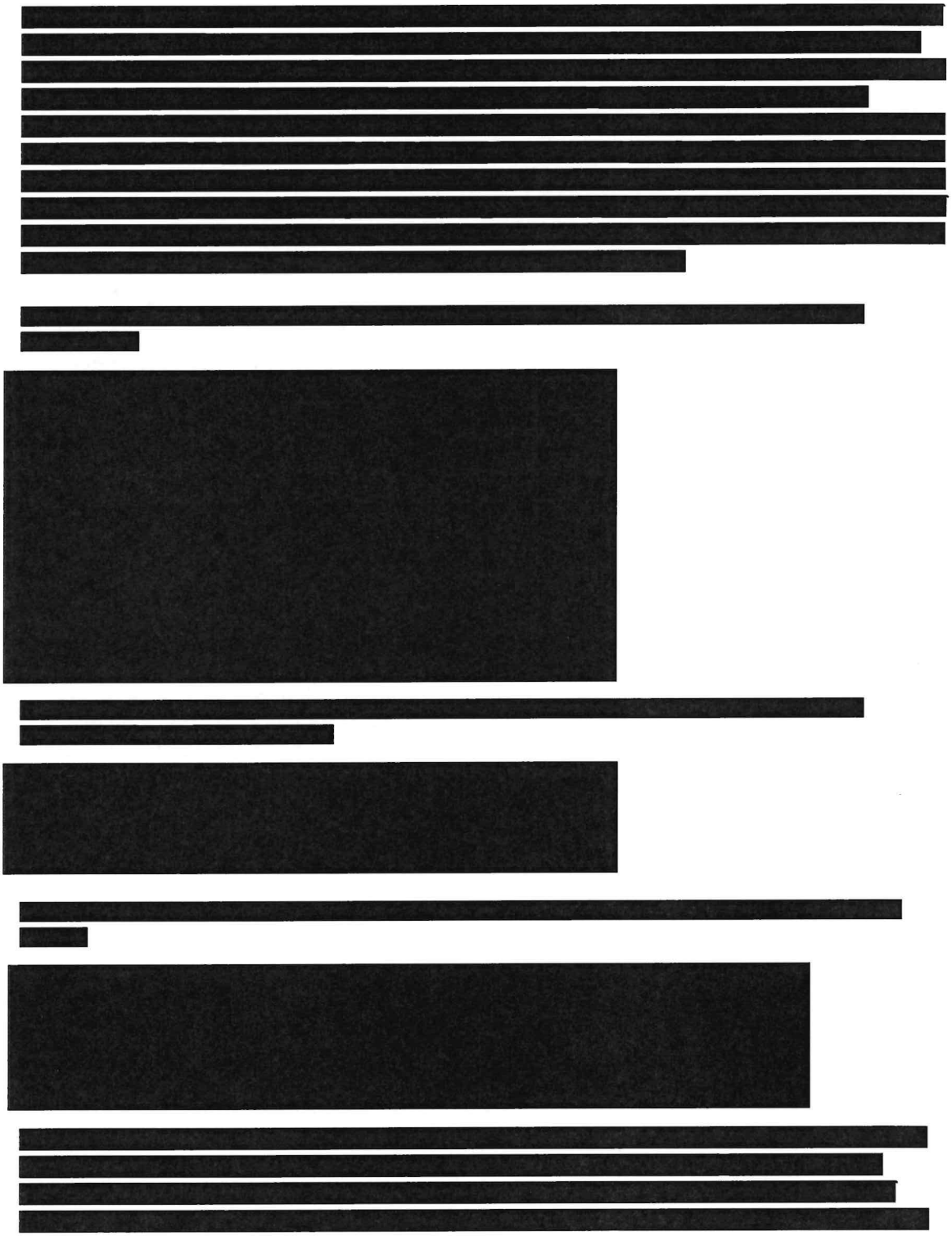
Adverse events and prior and concomitant diseases will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), although the dictionary will be modified to separately list cutaneous effects under or near the topical system (See **Section 9.4.3.4**). Statistical comparisons will be based on Fisher's exact test of all possible comparisons. All verbatim terms will be assigned to a Preferred Term (PT) and will be classified by primary System Organ Class (SOC) according to the MedDRA thesaurus., version 23.0 or higher. Prior and concomitant medications will be coded using the World Health Organization – Drug Reference List (WHO-DRL) Dictionary version March 1, 2020 or higher and classified according to at least the 3rd level Anatomical Therapeutic Chemical (ATC) Classification System level subgroup.

9.4 STATISTICAL ANALYSIS

The following is a brief description of the planned statistical analyses. A detailed SAP will be written after finalizing the protocol. The SAP may be updated before the end of data management activities or after a discussion of protocol deviations by the clinical team during the blind data review. The statistician may be provided with preliminary datasets that do not indicate group assignment.

9.4.1 Sample Size





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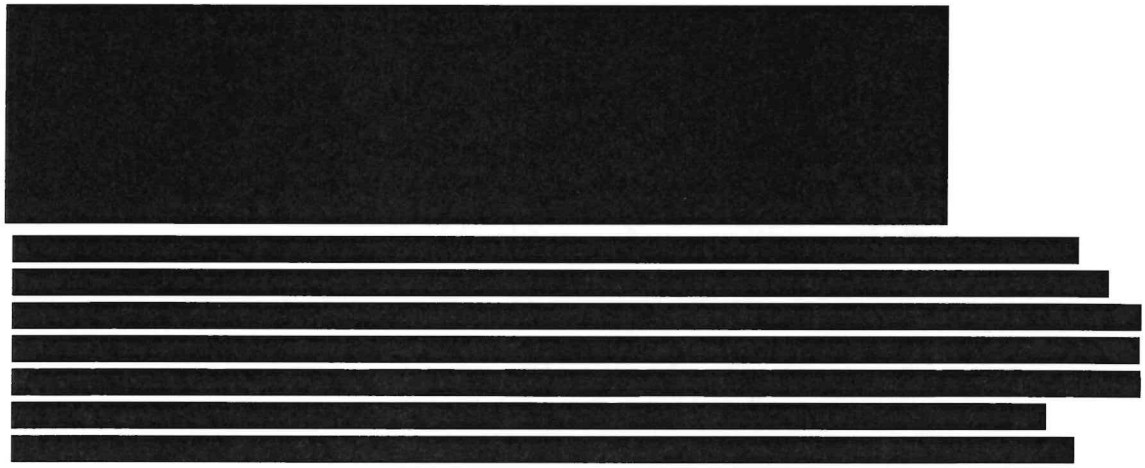

9.4.2 Population for Analysis

All participants who receive at least one application of the topical system will be subjected to the classic safety and efficacy analyses. All participants who receive at least one application of the topical system and have at least one blood draw that supports determination of plasma diclofenac concentration will be subjected to the pharmacokinetic analysis. Three subgroups of participants based on age (6-11 years old, 12-16 years old and 18-45 years old) will be analyzed separately and statistically compared. All participants in the efficacy analysis will be analyzed in the safety analysis. An evaluable participant population with adequate compliance and follow-up may also be analyzed. Any such secondary populations will be defined in a blind data review without knowledge of the age subgroups to which the participants belong.

9.4.3 Statistical Methods

9.4.3.1 Statistical Methods: General

In general, continuous variables will be presented as sample size, means, medians, standard deviations, range and 90% confidence interval (CI) of the means, while categorical variables will be presented as sample size, number of observations, percentage within each category and 90% CI of that percentage.

For all analyses, the primary comparison will be between the total pediatric population (i.e., the 6-11-year-old and 12-16-year-old subgroups combined) and the adult population. Secondary comparisons will include the pediatric subgroups with one another and each pediatric subgroup with the adult population.

For continuous variables, the three age subgroups will be compared using Analysis of Variance (ANOVA). Individual comparisons of the total pediatric population and the adult population and between the three age subgroups (6-11 years old, 12-16 years old and adult) will be presented without adjustment for multiple comparisons.

For binary categorical variables, pediatric and adult participants will be compared using the Fisher exact test. Individual Fisher exact tests will be used for all possible between-group comparisons.

For ordered categorical variables, pediatric and adult participants will be compared using the Cochran-Mantel-Haenszel (CMH) test. Individual CMH tests will be used for all possible between-group comparisons.

All individual time points will be separately analyzed. Where there are multiple values per patient, mixed models or general linear models with repeated measures adjustments will be used.

Two-sided significance levels (p values) less than 0.05 will be considered statistically significant but all p values will be reported to allow assessment of the reliability of those comparisons.

The primary endpoints are pharmacokinetic profile, adverse events, local tolerability and aPTT. The secondary endpoints are participant-reported pain scores, PI-reported global response to therapy and vital signs.

9.4.3.2 Statistical Methods: Primary Endpoint – Diclofenac Pharmacokinetic Profile

This study should yield a total of 300 plasma samples and associated diclofenac concentration data. The first blood draw will occur as close as possible to 24 hours after the first topical system application at Visit 1, while the second blood draw will occur at the EOS Visit. Participants with at least one topical system application and at least one blood draw will be included in the analysis. Blood draws obtained after the topical system has been removed will be excluded, but secondary analyses including cases with recent topical system removal may also be performed. In cases where the topical system has been cut and reduced in size, the observed diclofenac concentration will be adjusted accordingly for statistical analysis.

Because the plasma diclofenac concentration for each participant is expected to be obtained at steady state, population pharmacokinetic models are not appropriate. Diclofenac concentration will not be log-transformed and will be analyzed using mixed models with repeated measures and age subgroup (total pediatric population vs. adult population) as the primary covariate. Two-sided 90% CI (i.e., the two one-sided tests procedure) will be reported. If the upper and lower bound of the CI of the difference between any of the groups is less than 4 ng/mL (absolute), those groups will be considered equivalent.

Additional covariates that may be added to the model could include sex, height, weight, body mass index (BMI), time from first topical system application, and location of injury.

9.4.3.3 Statistical Methods: Primary Endpoint – Local Tolerability

This is an ordered categorical variable ranging from 0 to 6 and will be analyzed as described in the general statistical methods section.

9.4.3.4 Statistical Methods: Primary Endpoint – Adverse Events

Adverse events will be coded using MedDRA, which will be modified to split the SOC code for General Disorders and Administration Site Conditions into separate codes; one for General Disorders and another for Administration Site Conditions. This will be done to aggregate all skin conditions associated with topical system administration into a separate category. Statistical comparisons will be based on Fisher exact tests of the total pediatric population-adult population comparison as well as each of the three individual age subgroup comparisons. All SOC and PT codes will be analyzed.

9.4.3.5 Statistical Methods: Primary Endpoint – Activated Partial Thromboplastin Time (aPTT)

[redacted]

[redacted]in the present study, aPTT values from pediatric participants will be compared to adult participants, who will serve as the negative control.

[redacted]

Since children are expected, however, to have higher aPTT values than adults in the absence of treatment, an adjustment will have to be made for any comparisons between the pediatric and adult cohorts. To illustrate, it has been reported that adults have an upper boundary aPTT value of 38.2 seconds, while 6-10-year-olds and 11-16-year-olds have an upper boundary of 43.7 seconds and 46.1 seconds, respectively (**Table 9.4.3.5.2**).

Table 9.4.3.5.2: aPTT Values in Infants, Children and Adults*

	Age of Infant or Child vs Adult						
Parameter	**1 day**	**3 days**	**1-12 months**	**1-5 years**	**6-10 years**	**11-16 years**	**Adult**
aPTT	38.7	36.3	39.3	37.7	37.3	39.5	33.2

	34.3-44.8	29.5-42.2	35.1-46.3	33.6-46.3	31.8-43.7	33.9-46.1	28.6-38.2

* Values given are means + Range in seconds. Data obtained from Monagle P, Barnes C. Ignjatovic V, et al. Developmental haemostasis. Impact for clinical haemostasis laboratories. Thromb Haemost. 2006; 95:362-72.

Assuming an expected difference between pediatric and adult participants of 7.9 seconds (i.e., 46.1- 38.2), this study will have adequate power to reject the hypothesis of an aPTT excess difference in the upper bound (only) between pediatric and adult participants treated with the Licart topical system [redacted]

[redacted]

9.4.3.6 Statistical Methods: Secondary Endpoint – Pain Scores

Pain will be assessed by the participant using the Wong-Baker FACES scale during each study visit and twice each day in the Participant Diary. To use generalized linear model repeated measures analyses, these will be treated as continuous variables. The initial model will include age group, baseline pain score and assessment time. Comparisons will be made between the total pediatric population and the adult population as well as the three individual age subgroups using least-squares means. Other covariates may be added to the model as appropriate.

Study visits and Participant Diary pain scores will be analyzed separately. Pain scores for each individual visit will be compared using ANOVA as described in the section on general statistical methods.

[6] Lehman CM, Frank EL. Laboratory monitoring of heparin therapy: Partial thromboplastin time or anti-Xa assay? Labmedicine. 2009;40:47-51

9.4.3.7 Statistical Methods: Secondary Endpoint– Global Response to Therapy

Global response to therapy will be assessed by the PI or designee on a 5-point scale. The CMH test will be used to compare the total pediatric population and adult population as well as the three individual age subgroups.

9.4.3.8 Statistical Methods: Secondary Endpoint – Vital Signs

Vital signs will be analyzed using the methods described in **Section 9.4.3.1**.

9.4.3.9 Statistical Methods: Other Endpoints

Other variables including demographics, baseline characteristics and those collected during the EOS Visit will be analyzed using the methods described in **Section 9.4.3.1**.

9.4.4 Assumptions Required for Statistical Methods

Parametric methods of analysis are often considered to require the assumption of normality of the distributions. In particular, plasma diclofenac concentration distributions are expected to be skewed but, in this study, the sample size is high enough that the central limit theorem renders that assumption unnecessary.

9.4.5 Adjustment for Multiple Comparisons

For each variable, the primary comparison will be between the total pediatric population (i.e., the 6-11-year-old and 12-16-year-old subgroups combined) and the adult population. Comparisons of individual age subgroups are secondary. Therefore, adjustment for multiple comparisons will not be performed.

9.4.6 Missing Data

Missing values for pain scores may be imputed using multiple imputation methods if appropriate. Imputation will not be used for PK, aPTT or local tolerability data.

9.4.7 Interim Analysis

No interim analyses will be performed.

9.4.8 Sensitivity Analyses

Sensitivity analyses may be performed in order to examine the effects of missing values.

9.4.9 Subgroup and Covariance Analyses

Subgroup and covariance analyses may be performed in order to examine the effect of baseline variables on outcomes.

9.4.10 Individual Participant Data

All individual participant data recorded in the eCRF and all derived patient data used for statistical analyses will be provided in individual patient listings.

9.4.11 Protocol Deviations

A protocol deviation is any non-compliance with the clinical trial protocol, ICH GCP, or ancillary study requirements. The non-compliance may be on the part of the participant, the PI, or the clinical site personnel. Deviation from the protocol is prohibited, except in medical emergencies or in unforeseen, isolated instances in which minor deviations that do not increase the participant's risk or affect study endpoints are carried out.

It is the responsibility of clinical site personnel to be vigilant in identifying and reporting to the clinical monitor each protocol deviation that occurs during the study. Deviations that do not alter the benefit-risk profile, jeopardize participant safety or impact data integrity should be reported to the clinical monitor during the next monitoring visit. However, any deviation that does fall into one (or more) of these categories should be reported immediately to the clinical monitor. Following review of a deviation, the clinical monitor or sponsor designee will discuss the deviation with the PI and, if applicable, suggest corrective action to prevent recurrence. Any corrective action should be implemented promptly by the clinical site. All protocol deviations will be listed in the Blind Data Review document, wherein they will be classified as major or minor according to the impact on participant safety, data integrity, and efficacy assessments.

10 MONITORING AND ACCESS TO DATA

10.1 MONITORING

Monitoring of the clinical site will be performed to ensure the rights and well-being of study participants, that the reported study data are accurate, complete, and verifiable, and that the study is being conducted in compliance with the protocol and any amendments, the most recent ICH GCP guidelines, FDA guidance and any applicable local regulations.

[redacted]

Effective monitoring requires that the PI provide access to the clinical site facilities, applicable site personnel and source documents to the clinical monitor and/or sponsor designee(s). In addition, the PI (or designee) must be prepared to allocate sufficient time to the clinical monitor and sponsor designee(s) to facilitate completion of monitoring activities.

10.2 QUALITY CONTROL AND QUALITY ASSURANCE

The sponsor or designee will deliver a study training session to each clinical site prior to allowing enrollment of participants. Clinical site personnel not in attendance at this session must be trained by the sponsor, PI, or respective designee(s), prior to participation in study-related activities.

Clinical monitors will follow written Standard Operating Procedures (SOPs) to verify that the study is being conducted in accordance with the protocol and any amendments, ICH GCP guidelines and applicable regulatory requirements.

The PI is responsible for ensuring the quality of overall study conduct at their clinical site, including but not limited to data collection and entry, control of investigational product, biological sample collection, storage and shipment, and study document completion.

The PI will provide access to the clinical site facilities, applicable site personnel and source documents for monitoring and auditing by the sponsor and/or designee, and inspection by local and regulatory authorities. In addition, the PI or designee must allocate sufficient time to facilitate monitoring, auditing and/or inspectional activities.

10.3 SAFETY OVERSIGHT

No data safety monitoring board (DSMB) or other related committee(s) are planned for this study.

11 ETHICAL AND REGULATORY ASPECTS

11.1 DECLARATION OF HELSINKI

The study will be conducted in accordance with the Declaration of Helsinki (1996) and its amendments.

11.2 REGULATORY REQUIREMENTS

The sponsor will submit this protocol to the United States FDA in accordance with applicable regulatory requirements.

The sponsor will execute a Clinical Trial Agreement with each clinical site that participates in the study.

11.3 INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL

The protocol and ancillary study documents will be submitted to the responsible IRB(s) and an unconditional approval document that references the protocol must be received before starting the study; consequently, IP will not be shipped to clinical sites and clinical sites will not be permitted to begin enrolling participants until full approval has been obtained. Any subsequent protocol amendment and/or relevant information (e.g., serious adverse event) that becomes available after approval will be communicated to the IRB according to current effective guidance.

11.4 PROTOCOL AMENDMENTS

Neither the sponsor nor PI will amend this protocol without first obtaining agreement from the other party. Each protocol amendment must be signed and dated by the sponsor and PI. A major protocol amendment (e.g., informed consent form revision), except when it is necessary to eliminate apparent immediate hazard to the participant, must be approved by the IRB before implementation. A minor protocol amendment (e.g., editorial change) does not need to be approved by the IRB before implementation. Minor amendments will be communicated to the IRB as part of the next major amendment, as applicable. Certain protocol amendments may be submitted to FDA before implementation.

11.5 WRITTEN INFORMED CONSENT

IRB-approved documents, including the Participant Information Sheet and written informed consent form(s) describing the study intervention, procedures, and potential benefits and risks will be given to the participant and parent/legally authorized representative prior to enrollment. These concepts will also be delivered verbally by the PI (or designee), in addition to insurance coverage and procedures in the event of a study-related injury. The PI (or designee) will also inform the participant and parent/legally authorized representative that participation in the study is voluntary, that refusal to participate will not lead to loss of benefits or prejudice the relationship with the physician in any way, and that withdrawal from the study is possible at any time for any, or no reason.

The participant and parent/legally authorized representative will have adequate time to read and consider the consent form(s) and clarify unanswered questions before being asked to sign. The informed consent process and the date performed will be recorded in the source documents and the relevant consent form(s) will be fully executed before the participant undergoes any study-specific procedures. The original signed consent form(s) will be kept with the participant's study documents, while the parent/legally authorized representative and participant will be given a copy for future reference.

11.6 INSURANCE

[redacted]

11.7 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the PI, the sponsor(s) and their respective representatives. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the resulting data will be released to any unauthorized third party without prior written approval of the sponsor. The study will be registered with clinicaltrials.gov but participant-specific information will not be provided to or displayed on the website.

During and after the study, the participant's identity may become known to the sponsor or designee as part of routine monitoring or auditing procedures, or regulatory authorities as part of study review. Disclosure of a participant's identity to any other party will require prior agreement of the participant or parent/legally authorized representative, as applicable.

All research activities will be conducted in as private a setting as possible.

The sponsor, clinical monitor or other authorized representative(s) of the sponsor, representatives of the IRB or regulatory agencies may inspect all documents and records required to be maintained by the PI, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical site will permit access to such records. This information will be used by the sponsor to support development of the investigational product, and therefore may be disclosed to other investigators, development partners or regulatory authorities.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored by the statistician. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and management systems used by clinical sites and data management will be secured, and password protected. At the end of the study, all study databases will be de-identified and archived by the sponsor.

12 RECORD RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

After completion of the study and analysis of the data, the essential documents (ICH GCP E6, Chapter 8) will be stored in the Trial Master File in the sponsor's archive for at least 25 years according to new European Union (EU) regulations. The essential documents will also be stored in the Investigator Site File for at least 25 years. The participants' files (hospital charts, source documents, etc.) will be stored for the same period, or at least for the maximum period allowed by institutional policies, if not otherwise agreed to by the sponsor in writing.

Once the 25-year storage period has elapsed, the PI must contact the sponsor (contacts are provided in the Clinical Trial Agreement). The PI is not allowed to destroy the study related documents without prior written authorization from the sponsor. The sponsor will inform the PI when such documents no longer need to be retained.

12.1 BIOLOGICAL SAMPLES

Analyzed plasma samples and counter samples will be stored at the central and/or local laboratory according to a study-specific agreement between the sponsor and laboratory. The samples may be:

- used for reanalysis, as applicable;
- transferred to the sponsor; or
- destroyed.

If sample destruction is chosen at any time, the laboratory will provide the sponsor with a certificate of destruction.

Only the analyses described herein and agreed to by the participant following execution of the informed consent form will be performed, unless new analyses are approved by the IRB and new written informed consent obtained from the participant. The participant may ask to destroy their own stored samples at any time.

13 REPORTING

A clinical study report (CSR) will by prepared by the sponsor or designee according to ICH guidelines.

14 PUBLICATION POLICY

The data collected during the study will be the property of the sponsor. The sponsor is entitled to publish and/or present any results of this study at scientific meetings, and to submit these clinical trial data to regulatory authorities. The PI agrees to treat any unpublished information supplied by the sponsor or designee as confidential and ensure that confidentiality is maintained by all involved clinical site personnel.

The publication of any data derived from this study will be the result of a bilateral agreement between the PI and the sponsor. The sponsor has the right to review any manuscript about the study, and associated revisions will be delivered within 60 days of receipt. Revision of posters, abstracts, or any other similar publications will be performed within 15 days. For multicenter studies, the sponsor requires that the PI or designee does not publish any partial data before publication of the whole data set. The publication will neither disclose the identity of participants nor any intellectual property information.

15 RESPONSIBILITIES

The PI is responsible for personally supervising study conduct at their clinical site to ensure compliance with the protocol, ancillary study processes, ICH GCP, The Declaration of Helsinki, and applicable regulatory requirements. By signing this protocol, the PI attests to their understanding of, and commitment to upholding this responsibility.

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17 APPENDICES

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